

# ACE inhibition and AT<sub>1</sub> receptor blockers: efficacy and duration in hypertension

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Regardless of the time of day that it is measured—whether it be during the morning, the afternoon, the evening, and night time—there is a parallel, incremental, upward shift in blood pressure in the vast majority of hypertensive patients when compared with normotensive individuals. Intuitively it would therefore seem appropriate that strategies to reduce blood pressure should be effective throughout the 24 hour period in a consistent fashion (fig 1).

Epidemiological evidence reveals that the highest number of cardiovascular events occur in the early morning period and this corresponds to the time when there is a surge in blood pressure.<sup>1</sup> Blood pressure is not necessarily at its highest at this point, but there is a sharp rise from the inherently low levels during the night time period to those around the time of waking. It should be appreciated, however, that there are also other events that occur at this time such as changes in platelet aggregability and catecholamines. Importantly, as most patients take their antihypertensive medication in the morning, the surge in blood pressure also corresponds to the period with minimum pharmacological cover—that is, 24 hours post dose with a once a day regimen.

Epidemiological evidence also shows that blood pressure variability itself is an independent determinant of target organ damage. Thus, for any given level of average blood pressure, where variability around that mean is greater, the patient is likely to be more susceptible to evidence of hypertension related end organ damage.<sup>1</sup> Furthermore, there is evidence to support the contention that drug induced blood pressure variability may also be deleterious.

In patients who fail to show the “normal” circadian dip in night time blood pressure there is evidence of increased cardiovascular risk.<sup>1</sup> Initially this was demonstrated in cross sectional studies but had subsequently been confirmed in longitudinal analysis.

Finally, blood pressure measured over 24 hours much more closely predicts target organ damage than the clinic, office or isolated measurements that are mainly used for diagnoses. Once again the volume of cross sectional data has now been supported by the powerful evidence derived from the SAMPLE study.<sup>2</sup>

The SAMPLE study correlated beneficial reduction in left ventricular mass index (LVMI) during one year's treatment with the change in blood pressure over a 24 hour period, as compared to a single clinic blood pressure measurement.<sup>2</sup> There was a significant correlation between reduction in LVMI and changes in 24 hour blood pressure; however, there was no correlation with the isolated clinical blood pressure measurement (fig 2).

Based on this evidence, it is reasonable to suggest that optimal treatment of blood pressure requires strategies that:

- lower blood pressure consistently and fully throughout a 24 hour period;
- maintain the normal circadian pattern of blood pressure (that is, with a reduction in overnight blood pressure);
- do not increase blood pressure variability.

This strategy is supported by the Joint National Committee (JNC) VI guidelines which recommend the use of long acting anti-hypertensive formulations to ensure that control of hypertension is persistent and smooth rather than intermittent, and that protection is afforded against the abrupt rise in blood pressure after arising from overnight sleep.<sup>3</sup>

Despite the evidence and recommendations, blood pressure is not well controlled; this is well established for clinic blood pressure but, not surprisingly, is also true for 24 hour blood pressure control. This is illustrated by the PAMELA study that looked at three groups: normotensives; untreated hypertensives; and treated hypertensives.<sup>4</sup> As expected, in the untreated group there was a parallel, incremen-

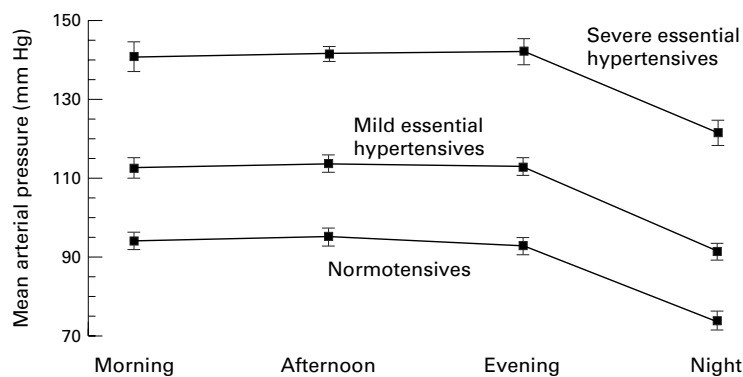


Figure 1 Intra-arterial blood pressure profiles over a 24 hour period.

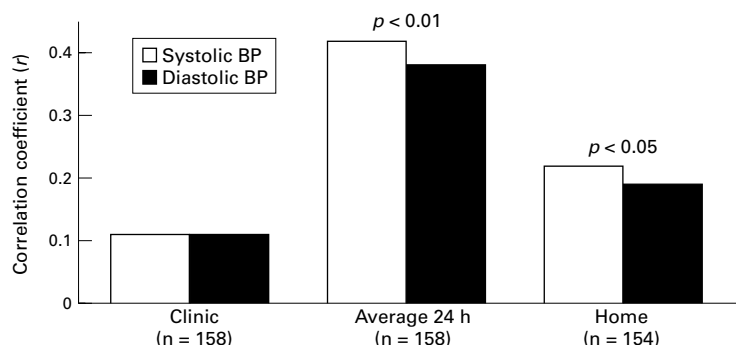


Figure 2 Correlation of change in left ventricular mass index and change in blood pressure after one year of treatment: SAMPLE study

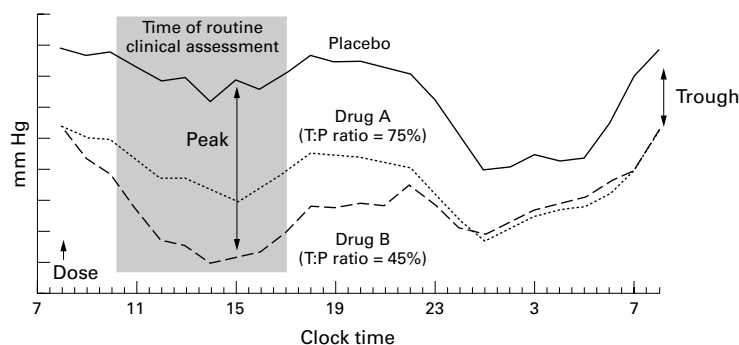


Figure 3 Relevance of trough:peak (T:P) ratios to 24 hour blood pressure control.

tal upward shift in blood pressure. However, the treated patients firstly did not have a sufficient lowering of blood pressure, and secondly, although in the first 16 hours there was a reduction in blood pressure, towards the end of the dosage interval blood pressure had returned to levels measured in untreated patients.

Interestingly, ambulatory blood pressure monitoring data with candesartan, as with many long acting antihypertensives, showed that there was a consistent reduction in blood pressure, which was sustained over the full 24 hour period.<sup>5</sup> More data are needed, however, to help define duration of effect when comparing different antihypertensive agents.

#### Trough:peak ratios

The JNC VI guidelines recommend the use of trough:peak ratios when differentiating between antihypertensive treatment. The guidelines state that the optimal formulation should provide 24 hour efficacy with a once daily dose with at least 50% of the peak effect remaining at the end of the 24 hours (fig 3).

This recommendation relates back to the US Food and Drug Administration (FDA) guidelines in the late 1980s that characterised the effects of antihypertensive agents at peak and trough.<sup>6</sup> The FDA recognised that, up until then too much emphasis had been placed upon the ability of treatment regimens to control blood pressure at a single time point at the end of the dosage interval, without due regard for the possibility that this "control" at this time might only have been achieved by virtue of a

profound fall in blood pressure around the time of peak response.

This can be highlighted by a comparison of the 24 hour blood pressuring profile of two hypothetical drugs, A and B (fig 3). If a single measurement of blood pressure was made at the end of the dosing period these two agents would be indistinguishable. They both reduce blood pressure by the same amount at trough, and on that basis, they could be considered acceptable for once daily administration. However, the drug with the higher trough:peak ratio (drug A) produces a much more consistent effect over 24 hours. In comparison, drug B produces a profound fall in blood pressure around the time of peak response which then tails off towards the trough effect at the end of the dose.

Interestingly, the time of peak response coincides with time when routine blood pressure assessments would be made in clinic. In response to such a large fall in blood pressure with drug B, a physician may reduce the dose, which would in turn lower the trough blood pressure reduction, resulting in poor blood pressure control around the time of awakening.

The importance of trough:peak ratios can be illustrated by the 24 hour blood pressure lowering profile of enalapril.<sup>7</sup> At lower doses of enalapril the trough:peak ratio is not very impressive. It increases to an acceptable ratio when the dosage is increased. In practice, the best way of administering this agent is twice daily which will produce a much more consistent effect at both trough and peak. In contrast, once daily dosing with lisinopril produces a much higher trough:peak ratio, which is not so dose dependent.<sup>8</sup> Furthermore a direct comparison of lisinopril and enalapril demonstrated superiority for lisinopril with respect to trough:peak ratio.<sup>9</sup>

#### Angiotensin II antagonists

Interest has recently focused on the 24 hour blood pressure lowering profiles of the newer angiotensin II antagonists. In a comparison of trough and peak blood pressure responses to candesartan 8 mg and 16 mg, and losartan 50 mg, there was an efficacy advantage in terms of the absolute blood pressure response at both doses of candesartan (this achieved significance at the 16 mg dosage).<sup>10</sup> In addition, there was less fluctuation between the peak and trough responses with candesartan compared to losartan. In terms of mean values, all three agents achieved trough:peak ratios in excess of the 50% threshold. However, looking at the lower extremity of the 95% confidence interval for these values, losartan only just achieved the 50% threshold (51%).

General practitioners usually perceive that angiotensin II antagonists are very well tolerated but not particularly potent. However, a recent study comparing candesartan, enalapril, and hydrochlorothiazide showed a clear benefit of candesartan at both six and 12 weeks of treatment (fig 4).<sup>11</sup> There was a significantly greater blood pressure response with candesartan when compared to either enalapril or hydrochlorothiazide, in both diastolic and

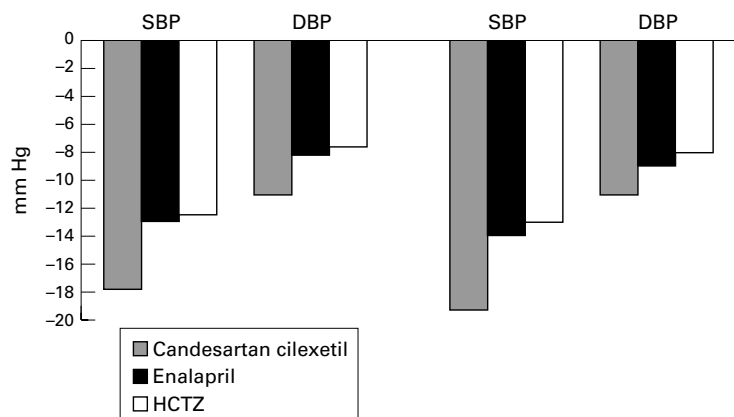


Figure 4 Blood pressure reductions with six and 12 weeks of treatment with candesartan cilexetil, enalapril, and hydrochlorothiazide (HCTZ).

systolic blood pressures. In addition, blood pressure control was achieved more consistently with candesartan than the other two agents.

#### Advantages of long acting agents

Agents that offer a long duration of action are attractive because many patients will inadvertently miss at least one dose of medication each week. In a study using 36 hours of ambulatory blood pressure monitoring to compare lisinopril with placebo, there was some loss of blood pressure control following a missed dose.<sup>12</sup> However, compared to placebo, there is a useful maintenance of blood pressure reduction with lisinopril.

A similar study compared candesartan and losartan.<sup>13</sup> It was a forced titration study so that the comparison at eight weeks was candesartan 16 mg and losartan 100 mg, with appropriate placebo control. After eight weeks of treatment there was a greater effect with candesartan over a 24 hour period which achieved significance for systolic blood pressure. Blood pressure monitoring over a 36 hour period revealed that the shorter acting agent, losartan, had a relatively rapid offset of blood pressure control, while the longer acting agent, candesartan, sustained its effect. This finding was also supported by the clinic blood pressure recordings 48 hours post dose which revealed that while the reductions with losartan were not significantly different from placebo, candesartan maintained a significant and clinically relevant reduction in blood pressure at this time.

#### Conclusion

The evidence therefore suggests that the maximal benefits of antihypertensive treatment are likely to be achieved with regimens that provide consistent blood pressure control over the recommended dosage interval and have intrinsic

#### Trial acronyms

PAMELA: Pressione Arteriose Monitorate E Loro Associazioni

SAMPLE: Study on Ambulatory Monitoring of Blood Pressure and Lisinopril Evaluation

long duration of action. This will provide good therapeutic coverage despite inadequate patient compliance.

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